REMARKS

Reconsideration of the rejection of claims 39-41, 43-49, 51 and 61 and the objection to claim 63 are respectfully requested in view of the following remarks.

Claim Amendments

New claims 64-76 have been added, which claims each recite individually one of the 13 compounds specifically named in the selection of claim 48. Support for these new claims is thus clear, and entry of this amendment is respectfully requested. Following entry of this amendment, claims 39-41, 43-49, 51, 61 and 63-76 are pending in this application.

Claim Rejections – 35 USC § 102

Claims 39-41, 43-49, 51 and 61 have been newly rejected under 35 U.S.C. § 102(b) as being anticipated by either of the newly cited Sinyak *et al.* and Karminski *et al.* Chemical Abstracts References. It is understood that the Examiner's position is:

- that Karminski *et al.* discloses compounds which are encompassed by the present generic claims when Zb is O or S, ring C is a quinazolinyl ring, and R^2 is H (when it is $-X^1R^5$ where X^1 is a bond and R^5 is H); and
- that Sinyak *et al.* discloses compounds which are encompassed by the present generic claims when Zb is S, ring C is a quinolinyl ring, and R^2 is H (when it is $-X^1R^5$ where X^1 is a bond and R^5 is H).

This ground for rejection is respectfully traversed with respect to both cited documents.

First of all, the Examiner's attention is directed to the full English language copies of the articles corresponding to the Karminski *et al.* and Sinyak *et al.* abstracts, which were previously formally cited in this application (and copies thereof provided) with the Information Disclosure Statement filed October 23, 2003. The full articles were listed as documents VR and WR, respectively, on the accompanying form PTO-1449 dated October 23, 2003 as follows:

VR: Karminski et al., The Synthesis of Some Quinazoline Derivatives and Their Biological Properties; J. Environ. Sci. Health, Vol B18, 1983, pp. 599-610

WR: Sinyak, et al., Synthesis and Biological Properties of Derivatives of 4-Heterylmercaptoquinazoline, Zaporozh'e Medical Institute pp. 103-106, translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 2, Feb. 1986, 168-171, original article submitted 12/29/84

Consideration of both documents by Examiner Truong was acknowledged on the initialed copy of the October 23, 2003 form PTO-1449 returned to the undersigned with the Action mailed January 14, 2004. However a further copy of each document is attached for the Examiner's convenience, **but not again listed** on the form PTO-1449 to avoid duplication.

Secondly, it is respectfully submitted that neither reference (in full or in Abstract form) discloses any compound that is recited in, or falls within the generic scope of, any claim pending in this application. Most particularly, as the Examiner recognizes, the compounds of both references require a hydrogen at the position of R^2 (the 7-position) on the quinazoline ring of the presently claimed compounds. However, hydrogen is specifically *excluded* from the definition of R^2 by the proviso at the end of claim 39 (see page 10 above at line 15). All other claims dependent on claim 39 therefore incorporate this proviso as well. Accordingly, no claim presently pending in this application either describes or generically encompasses any compound disclosed in either the Karminski *et al.* or the Sinyak *et al.* reference. Since there is no anticipation, it is respectfully requested that the rejection under section 102(b) be withdrawn.

It should be noted that this proviso, removing hydrogen from the permissible values for R^2 in formula (II), was present in the PCT application of which the current application is the US National Stage. See, *e.g.*, the specification description of compounds of formula (II) at page 51, line 28 through page 52, line 17 (specifically at page 52, lines 11-12), and in original claim 9 at page 328, line 26. Original compound claim 9 drew on some definitions from original "use" or method claim 1. Compound claim 9 was rewritten in independent form as new compound claim 39 presented with the Preliminary Amendment filed May 6, 2002, in which, *inter alia*, definitions from original claim 1 were directly incorporated into compound claim 39, and this proviso from original claim 9 was retained.

Claim Rejections – 35 USC § 103

Claims 39-41, 43-49, 51 and 61 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over the Karminski *et al.* or the Sinyak *et al.* Chemical Abstracts. As the basis for this rejection, the Examiner specifically notes:

> Where not anticipated, one would be motivated to prepare the present compounds from within the generic teachings of the references and/or to prepare the present homologs and isomers of the specific compounds of the references with the reasonable expectation of obtaining additional compounds for the uses in the references.

(Action at page 3). It thus is understood that this rejection starts from the premise that at least claim 39 is anticipated by the cited references, and then concludes that the remaining claims, "where not anticipated," are rendered obvious as encompassing homologues and isomers of the specific reference compounds. With this understanding it is believed that the above comments, which demonstrate there is no basis for the anticipation rejection, likewise remove the underlying premise for this obviousness rejection. Withdrawal of this obviousness rejection is therefore respectfully requested.

If, nevertheless, the Examiner still asserts that that one or more of these claims are rendered obvious by these references, this rejection is respectfully traversed.

It is difficult for Applicant to meaningfully address specific bases for this rejection in that the Examiner has not pointed to any "generic teachings of the references," and no particular homologs or isomers are identified. In fact, it is respectfully submitted that there is no generic teaching in these references, since each reference identifies only a group of specific compounds: 27 specific quinazoline compounds in Karminski *et al.* and 9 specific quinazoline compounds Va through Vi in Sinyak *et al.*

Karminski *et al.* have synthesized 27 "quinazoline derivatives" to explore their plant protection capabilities. Fifteen of the compounds are mono-substituted at position 4; seven compounds are bis-substituted at positions 2 and 4; and five compounds are "quadruply-substituted" at positions 2, 4, 6 and 8 of the quinazoline ring. While all 27 compounds are 4-position substituted, only two of the 27 compounds are substituted at the 4-position (or at any position, for that matter) with a "9 or 10-membered heteraromatic bicyclic moiety which

contains 1-3 heteroatoms independently selected from O, N and S" as required for ring C of the present claims. These are compounds 7 and 8, the two "mono-substituted" compounds illustrated in the corresponding Abstract, which have only a hydrogen at the 7-position, whereas the present claims require a non-hydrogen substituent as R^2 at this position. In fact, *all positions* (other than the 4-position) of the quinazoline ring of these two Karminski *et al.* compounds have *only* a hydrogen and no other substituent. Therefore, it is not seen how any of the presently claimed compounds could be said to be an isomer of these Karminski *et al.* compounds if there is no substituent to move around the ring.

Moreover, it is not believed that a skilled chemist would characterize any of the presently claimed compounds as a "homolog" of either of the Karminski *et al.* compounds. Even to the extent that the R^2 substituent might be a C_{1-3}alkyl, the addition of an alkyl group where none existed before, or the removal of an entire alkyl substituent so that none is present, are not traditionally considered to be adjacent homologues, which traditionally would apply only to changing the length of the alkyl substituent by a methylene, not adding or removing the entire group.

In any event, the Karminski *et al.* reference provides no motivation whatsoever for the skilled person to modify any of the 27 compounds to find compounds with improved plant biological properties, since all of the compounds were deemed to be failures. See, for example, the Conclusion of the full reference which states:

> All 27 tested quinazoline derivatives have not fulfilled the accepted criteria for the biological tests which excludes them from further field experiments which would be the third stage of the screening.

(Karminski *et al.* at page 610). The Abstract confirms this conclusion, stating that "all were ineffective except for 4-chloroquinazoline, which showed mild fungicidal activity." Thus, even if there might be motivation to carry on further with these experiments, the skilled person would likely start, if at all, with the 4-chloroquinazoline (which wholly lacks the essential 4-position C ring of the present claims, linked by –O- or –S-), rather than the two mono-substituted compounds cited by the Examiner that were characterized as being "ineffective."

Thus, whether or not considered isomers or homologues, the skilled person would be directed away from compounds 7 and 8 that are closest to those presently claimed, and there is no suggestion or guidance that would lead him or her to modify the even more distant but mildly effective 4-chloroquinazoline compound to a structure that falls within the scope of the present claims. Note in particular that "ineffective" compounds 7 and 8 were already made by the authors by modifying the mildly effective 4-chloroquinazoline compound, but with unfavorable results, which would eliminate any motivation to try this unsuccessful route again.

Similarly, the Sinyak *et al.* reference does not raise a *prima facie* case of obviousness. Sinyak *et al.* discloses nine specific compounds, only two of which have a substituent on the 4-position of the quinazoline ring that meets the definition of ring C of the present claims, linked by -S-. Neither of these two compounds (compounds Va and Vb) has any other substituent on the quinazoline ring. Thus, there necessarily is a hydrogen at the 7-position, which is not a permissible value for R^2 of the present claims, and there is no substituent at any other position of the quinazoline ring that could give rise to an assertion of ring isomerism. Moreover, for the reasons discussed above with respect to the Karminski *et al.* reference, it is not seen that a skilled chemist would characterize any of the presently claimed compounds as a "homolog" of either of the Sinyak *et al.* compounds, even to the extent that the R^2 substituent might be chosen to be a C_{1-3}alkyl.

In any event, the questionable activity and/or toxicity of compound Va and Vb relative to other more distant compounds as discussed in the full article would likely lead the skilled person away from compounds Va and Vb, and there is no suggestion or guidance that would lead such person to modify these or any other disclosed compound to form a structure that falls within the scope of the present claims, with any expectation of success.

Again, the homology and isomerism noted by the Examiner is not seen between presently claimed compounds and the specific compounds of the Karminski *et al.* and Sinyak *et al.* references, and no other suggestion or motivation is seen to select the closest compounds of these references and to modify them the manner that would be required to make compounds within the scope of the presently claimed compounds. Therefore, it is

respectively submitted that a *prima facie* case of obviousness has not been made. Moreover, decisions of the Federal Circuit have cautioned against making generalizations from characterizations, such as isomers and homologues, as giving rise to *prima facie* obviousness. See, for example, the Federal Circuit decision in *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985):

> When chemical compounds have "very close" structural similarities and similar utilities, without more a prima facie case may be made. See for example In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977) (adjacent homologues and structural isomers); In re May, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978) (steroisomers); In re Hoch, 428 F.2d 1341, 166 USPQ 406 (CCPA 1970) (acid and ethyl ester). When such "close" structural similarity to prior art compounds is shown, in accordance with these precedents the burden of coming forward shifts to the applicant, and evidence affirmatively supporting unobviousness is required.
>
> Analysis of those circumstances in which a prima facie case has or has not been made in view of the degree of structural similarity or dissimilarity, or the presence or absence of similar utility between the prior art compound and that of the applicant, has inspired generations of applicants, courts, and scholars. Upon review of this history, we have concluded that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other.

226 USPQ at 871-72 (emphasis added).

It is submitted that the circumstances detailed above with respect to the two cited references make this a case where "that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other," in accordance with the *Grabiak* decision, and this rejection therefore should be withdrawn.

Allowable Subject Matter – Objection to Claim 63

Method claim 63 has only been objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form. Inasmuch as the base claims are believed to be in condition for allowance for the reasons discussed above, this objection to claims 63 should be overcome without need for amendment.

Information Disclosure Statement

The Examiner's attention is called to the further Information Disclosure Statement that is being filed together with this Response, which is accompanied by a form PTO-1449 and a copy of the non-US patent documents listed thereon. It is respectfully requested that these documents be considered, and that such consideration be acknowledged by the Examiner's initials where indicated and return of an initialed copy of the form PTO-1449 to the undersigned.

Request for Acknowledgement of Certified Priority Document

Applicants respectfully request clarification of the status of the certified priority document, and formal acknowledgement that a certified copy of the priority document has been received in this file in support of Applicants' claim for foreign priority of EPO 99400305.1 filed February 10, 1999. The Notification of Missing Requirements mailed December 6, 2001 lists the Priority Document as one of the items submitted to the U.S. Patent and Trademark Office. However, the Office Action Summary mailed January 14, 2004 acknowledges the claim for foreign priority, but indicates that the certified copy of the priority document has *not* been received.

The certified priority document was timely submitted to the International Bureau (stamped received May 4, 2000), and the International Bureau should have forwarded a copy to the U.S. Patent and Trademark Office as a matter of course. Inasmuch as it appears that a copy of this certified priority document should be present in this application, acknowledgement of the same is respectfully requested. However, if for some reason a copy is not now in the file, it is respectfully requested that Examiner notify the undersigned as to what action is being taken to investigate the location of this document and/or to obtain a copy from the International Bureau, so that Applicants can be certain that a copy is present in the file by the time the Issue Fee is paid herein.

Conclusion

In view of the above remarks, it is believed that all grounds for rejection and/or objection have been overcome. Therefore, the allowance of all claims, including new claims

64-76, is believed to be in order, and a Notice to that effect is respectfully solicited. If, nevertheless, the Examiner believes that there are any remaining outstanding grounds for rejection, it is requested that the Examiner telephone the undersigned to resolve of any such issues in order to expedite the prosecution of this application to allowance.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
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Date: March 7, 2005 By: _____

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